Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Integrase Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

This class of antiretroviral (ARV) drugs inhibits integrase, the viral enzyme that catalyzes the two-step process that inserts HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides at both ends of one strand of HIV DNA and a final "strand transfer" step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step of the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects reverse transcription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

Bictegravir (BIC)

(Last updated December 7, 2018; last reviewed December 7, 2018)

There are insufficient human data on the use of bictegravir in pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

Animal Studies

Carcinogenicity

Bictegravir was not genotoxic or mutagenic *in vitro*.[1]

Reproduction/Fertility

Bictegravir did not affect fertility, reproductive performance, or embryonic viability in male and female rats at exposures (area under the curve [AUC]) that were 29 times higher than those seen in humans receiving the recommended dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at bictegravir exposures (AUC) of up to approximately 36 times (rats) and 0.6 times (rabbits) the exposures seen in humans receiving the recommended dose. Spontaneous abortion, increased clinical signs (e.g., fecal changes, thin body, and cold-to-touch), and decreased body weight were observed at a maternally toxic dose in rabbits (i.e., 1000 mg/kg/day; approximately 1.4 times higher than human exposure at the recommended dose).[1]

Placental and Breast Milk Passage

No data on placental passage are available for bictegravir. In a pre/postnatal development study conducted in rats, bictegravir was detected in the plasma of nursing rat pups on postnatal day 10, likely due to the presence of bictegravir in milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of bictegravir have been reported in pregnant women.

Placental and Breast Milk Passage

No data are available on the placental or breast milk passage of bictegravir in humans.

Teratogenicity/Adverse Pregnancy Outcomes

No data are available to inform the risk determination for birth defects following bictegravir exposure.

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Bictegravir/ Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* **Note:** BIC is not available as a single-entity formulation.	BIC/FTC/TAF (Biktarvy): • BIC 50 mg plus FTC 200 mg plus TAF 25 mg tablet	Standard Adult Dose • 1 tablet once daily with or without food Dosing in Pregnancy: • There is insufficient data to make a dosing recommendation. PK in Pregnancy: • No PK studies have been reported in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF).	No data are available on placental transfer of BIC. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. To maximize BIC absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

Key to Acronyms: ARV = antiretroviral; BIC = bictegravir; FTC = emtricitabine; FDC = fixed-dose combination; PK = pharmacokinetic; TAF = tenofovir alafenamide

References

1. Bicitegravir/emtricitabine/tenofovir alafendamide fumarate (Biktarvy) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf.